"Express Mail" Label No. EV 529 872 379 US
Date of Deposit: 8 June 2005

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Address" service under 37 CFR 1.10 on the date indicated above and is addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By: _____
Jordan Magat

PATENT
Attorney Docket No.: 021305-003500US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: George Tidmarsh	Examiner: Raymond J. Henley III
Application No.: 10/759,337	Art Unit: 1614
Filed: January 16, 2004	SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98
For: TREATMENT OF BENIGN PROSTATIC HYPERPLASIA	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The references cited on the attached PTO/SB/08A and PTO/SB/08B forms are being called to the attention of the Examiner. Copies of the references are enclosed. It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR 1.97(g) and (h), no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information, and no inference should be made that the information and references cited are, or are considered to be, material to patentability because they are in this statement. No inference should be made that the information and references cited are prior art merely because they are in this statement.

For the convenience of the Examiner the listed references are briefly characterized below. However, Applicant understands the Examiner will review and form his own opinion about the contents of each.

A. References describing a relationship between prostate epithelial cells and BPH.

- References AJ (Isaacs and Coffey); AK (Hudson *et al.*); AL (Collins *et al.*); AM (Giri and Ittmann); and AN (Castro *et al.*) relate to possible roles of prostate epithelial cells in BPH.

B. References relating to treatment of cancer or prostate cancer.

- References AP (Dudak *et al.*); AQ (Bloch *et al.*); and AR (Benz *et al.*) describe experiments in which lonidamine was tested for activity against prostate cancer cells. References AO (Boccardo *et al.*) and AI (Ireland Pat. Specification No. 54256 "Use of Lonidamine in Cancer") describe administration of lonidamine to human cancer patients.

- References AB (US 5,827,887); AC (WO 98/10781); AD (WO 9714670); AE (WO 9640142); AH (Canada patent application No. 2,206,198); and AS (Eri *et al.*) each describe agents (biphenyl compounds, leuprolide, lignan derivatives, pyridine derivatives, substituted benzoylguadines, and cetrorelix, respectively) purported to be useful for treatment of cancer and one or more other diseases other than cancer (*e.g.*, BPH, cardiac infarct, shock, stroke, atherosclerosis, diabetic complications, pulmonary, hepatic or renal fibrosis, hypertension, disorders of lipid metabolism, acne, androgenic alopecia, hirsutism, seborrhea, psoriasis, *etc.*).

C. WO 2004/064735

- Reference AF (WO 2004/064735) is a PCT patent application corresponding to the instant U.S. application.

- Reference AT is the International Search Report and Written Opinion for WO 2004/064735. The Written Opinion refers to U.S. Pat. No. 5,260,327 (Kim *et al.*) which is of record in the instant application, having been submitted in the information disclosure statement filed November 3, 2004. The Kim *et al.* patent describes the use of lonidamine in combination with hyperthermia and radiation to treat cancer. The Kim *et al.* patent did not refer to using lonidamine for treatment of BPH.

D. WO 2004/064736

- Reference AG is commonly assigned PCT patent application WO 2004/064736, filed on the same day and with the same priority claim as the instant application. WO 2004/064736 is directed to the use of energolytic agents (agents that interfere with cellular energy metabolism) for treatment of BPH and teaches that lonidamine and londamine analogs are examples of energolytic agents.

- Reference AU is the International Search Report and Written Opinion for WO 2004/064736.

References AA (US Pat. No. 3,895,026/Palazzo); Grima *et al.* (of record, submitted in the November 3, 2004, information disclosure statement); AW (Shidaifat *et al.*); and AX (Chang) were cited in the Written Opinion. The following remarks relate to these references and the comments of the International Searching Authority (ISA):

Reference AA (Palazzo/US Pat. No. 3,895,026) discloses lonidamine and other substituted 1-benzyl-1H-indazole-3-carboxylic acids and discusses their potential use as antispermatogenic agents. The Palazzo reference states that lonidamine is a member of a broader class of compounds, and that some members of the class "provoke a neat atrophy of the seminal line of the testes without causing other toxic effects." The ISA characterized this statement concerning seminal line atrophy, as "clearly suggesting that an energolytic agent such as lonidamine could treat/decrease the size of benign prostatic hyperplasia [*sic*] . . . ." However, the seminal line is not part of the prostate, and if the ISA had any rationale or information explaining why BPH and seminal line atrophy are in any way related, it was not evident to the Applicant. The ISA's assertion that treatment of BPH was *suggested* by the Palazzo patent is demonstrably incorrect, as the Palazzo patent specifically delineates the uses contemplated for the disclosed carboxylic acid derivatives. For example, the Palazzo patent states: "These [properties] suggest the use of those substances as antispermatogenics in human and veterinary medicine and presumably also in order to reduce the multiplication of harmful insects" (col. 2). The Palazzo patent also mentions the potential use of these compounds to inhibit ovulation in females and the potential use of some 1-benzyl-1H-indazole-3-carboxylic acid derivatives to treat inflammatory and degenerative diseases (see col. 2). There is no reference in the Palazzo patent of using any agent to treat BPH.

The Grima *et al.* reference describes reversible inhibition of spermatogenesis in rats following administration of AF2364, a lonidamine analog being investigated as a contraceptive. The ISA noted in the Written Opinion that the Grima *et al.* reference reports morphological changes within the prostate columnar epithelial cells of treated rat prostate in comparison to the control, where "the epithelial cells surrounding the lumen were decreased in height and were less convoluted than the control." The significance attributed by the ISA to the Grima *et al.* reference is not clear to the Applicant from the Written Opinion. It is possible the decrease in *height* of epithelial cells in treated animals was considered relevant by the ISA and perhaps was equated with a decrease in prostate size. However, the Grima *et al.* reference characterized the effect of lonidamine on prostate size as resulting in "slight variations [in weight] . . . at only a few time points" (see the last line of p. 1503). Further, it appears from Figure 5C of the Grima *et al.* reference that, if anything, ventral prostate weight trended *higher* (although perhaps not

significantly) in the treated animals. Nothing in the Grima *et al.* reference referred to the use of lonidamine for treatment of BPH.

Applicant is aware of other published studies, not cited by the ISA, investigating the potential use of lonidamine or analogs for contraception and providing data on prostate size. Lobl (reference AV) describes research in rats on use of lonidamine (referred to as "DICA") as an antifertility agent. The Lobl reference reports that administration of lonidamine significantly reduced testicular weight, but that "[n]either single doses . . . nor five daily doses . . . [of lonidamine] reduced seminal vesicle, ventral prostate or body weights of male rats" (see Abstract; also see Tables 2 and 3). Heywood *et al.*, 1981 (of record, submitted in the November 3, 2004, information disclosure statement) reported that in toxicology studies of 1-substituted-indazole-3-carboylic acids as potential male contraceptives, rats treated with lonidamine or tolnidamine (a lonidamine analog) had lower testes, prostate and seminal vesicle weights than control animals (p. 93). The Heywood *et al.* reference did not refer to any application of lonidamine in BPH. Lobl *et al.*, 1981 (of record, submitted in the November 3, 2004, information disclosure statement) also studied the contraceptive potential of lonidamine and analogs. In Table III of the Lobl *et al.* reference, the reported mean ventral prostate weights in rats treated with a lonidamine analog (tolnidamine) are lower 10 days after treatment than in untreated animals (also see Figure 7). However, as evident from the *absence* of any superscript denoting significance of the ventral prostate values (*i.e.*, *a*, *b* or *c*), the Lobl *et al.* reference did not regard the change in mean weight as statistically significant (compare the indication in Tables I, II, and III of statistically significant changes in serum ABP, testicular ABP, epididymal ABP and testis weight). In addition, the Lobl *et al.* reference notes elsewhere "In view of the apparent differences in the effects of lonidamine and tolnidamine in the above studies, it was of interest to compare the potency of these agents with that of the structurally related parent compound, AF 312/TS. When the compounds were administered at 60, 100 and 500 mg/kg, no significant effects were seen on body, ventral prostate or seminal vesicle weights." (p. 68). The Lobl *et al.* reference did not refer to use of lonidamine or analogs for treatment of BPH.

- References AW (Shidaifat *et al.*) and AX (Chang *et al.*) were also cited in the Written Opinion for WO 2004/064736. These references describe gossypol, a compound structurally dissimilar from lonidamine and with different activities. Gossypol, lonidamine, and a variety of other compounds are identified in WO 2004/064736 as examples of various types of energolytic agents.

Reference AV (Shidaifat *et al.*), reports that gossypol arrested human benign prostatic hyperplastic cell growth *in vitro* at the G0/G1 phase of the cell cycle, and proposed gossypol as a potential chemotherapeutic agent for BPH. Although the Shidaifat *et al.* reference attributes a number of

distinct activities to gossypol (*e.g.*, inhibition of 5α-reductase, inhibition of 3α-hydroxysteroid dehydrogenase, inhibition of protein kinase-C; inhibition of adenylate cyclase, and effects on topoisomerase and DNA polymerase-α) the reference proposes that the effect of gossypol on prostate cells is due to induction of TGF-β_1 expression. TGF-β_1 is an inhibitory growth factor capable of arresting cells in the G1 phase of the cell cycle. The Shidaifat *et al.* reference did not refer to the use of lonidamine for treatment of BPH.

Reference AX (Chang *et al.*) reports that gossypol induces expression of the enzyme spermidine/spermine N1-acetyltransferase (SSAT) in canine prostate epithelial cells and proposed gossypol as a potential chemotherapeutic agent for BPH. The Chang *et al.* reference reports that progression of canine prostate epithelial cells into the S phase is stimulated by spermadine, and speculates that enhanced expression of SSAT (which plays a role in catabolism of spermadine) may deplete the pool of intracellular polyamines, thereby inhibiting cell growth. In addition to inducing SSAT expression, the Chang *et al.* reference indicates that gossypol's other activities include inhibiting respiration, suppression of testicular steroid production, inhibition of 5α-reductase, and inhibition of aromatase. The reference also speculates that some effects of gossypol may be due to the fact that the compound may "potentially simultaneously inhibit 5α-reductase and aromatase activities, thus preventing the conversion of testosterone to the two synergistic steroids DHT and estradiol-17β." The Chang *et al.* reference did not refer to the use of lonidamine for treatment of BPH.

This IDS is being filed before the mailing date of the final Office Action or Notice of Allowance. Please charge the IDS fee of $180 to Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,

Randolph Ted Apple
Reg. No. 36,429

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422

PTO/SB/08A (08-03)

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/759,337
Filing Date	January 16, 2004
First Named Inventor	Tidmarsh, George
Art Unit	1614
Examiner Name	Raymond J. Henley III
Attorney Docket Number	021305-003500US

U.S. PATENT DOCUMENTS+

Examiner Initials*	Cite No.[1]	Document Number Number Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-3,895,026	07-15-1975	PALAZZO et al.	
	AB	US-5,827,887	10-27-1998	GOURVEST et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]	Number[4]	Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	AC	WO	98/10781	A1	03-19-1998	Asta Medica		☐
	AD	WO	97/14670	A1	04-24-1997	Kanoldt Arzneimittel		☐
	AE	WO	96/40142	A1	12-19-1996	Pfizer, Inc.		☐
	AF	WO	2004/064735	A2	08-05-2004	Threshold Pharmaceuticals		☐
	AG	WO	2004/064736	A2	08-05-2004	Threshold Pharmaceuticals		☐
	AH	CA	2,206,198		05-27-1997	Hoechst Aktiengesellschaft		☐
	AI	IE	54256		08-02-1989	A.C.R.A.F.		☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] **Applicant's** unique citation designation number **(optional)**. [2] Kind Codes of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449B/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)* Sheet 2 of 2	*Complete if Known*	
	Application Number	10/759,337
	Filing Date	January 16, 2004
	First Named Inventor	Tidmarsh, George
	Art Unit	1614
	Examiner Name	Raymond J. Henley III
	Attorney Docket Number	021305-003500US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	AJ	ISAACS et al., "Etiology and disease process of benign prostatic hyperplasia" Prostate Suppl., 2:33-50 (1989).	
	AK	HUDSON et al., "Proliferative heterogeneity in the human prostate: evidence for epithelial stem cells" Lab Invest., 80:1243-1250 (2000).	
	AL	COLLINS et al., "Benign prostatic stromal cells are regulated by basic fibroblast growth factor and transforming growth factor-beta 1" J Endocrinol., 151:315-322 (1996).	
	AM	GIRI et al., "Interleukin-8 is a paracrine inducer of fibroblast growth factor 2, a stromal and epithelial growth factor in benign prostatic hyperplasia" Am J Pathol., 159:139-147 (2001).	
	AN	CASTRO et al., "Interleukin-8 expression is increased in senescent prostatic epithelial cells and promotes the development of benign prostatic hyperplasia" Prostate, 60:153-159 (2004).	
	AO	BOCCARDO et al., "Phase II study with lonidamine in the treatment of hormone-refractory prostatic cancer patients" Tumori, 78:137-139 (1992).	
	AP	DUDAK et al., "Enhancement of radiation response of prostatic carcinoma by lonidamine" Anticancer Res., 16:3665-3671 (1996).	
	AQ	BLOCH et al., "Enhancement of hyperthermic toxicity by lonidamine in the Dunning R3327G rat prostatic adenocarcinoma" Prostate, 24:131-138 (1994).	
	AR	BENZ et al., "Lactic dehydrogenase isozymes, 31P magnetic resonance spectroscopy, and in vitro antimitochondrial tumor toxicity with gossypol and rhodamine-123," J Clin Invest. 79:517-523.	
	AS	ERI et al., " Effects on the endocrine system of long-term treatment with the luteinizing hormone-releasing hormone agonist leuprolide in patients with benign prostatic hyperplasia" Scandinavian Journal of Clinical and Laboratory Investigation, 56: 319-325 (1996).	
	AT	International Search Report and Written Opinion for PCT/US2004/001141 (WO 2004/064735)	
	AU	International Search Report and Written Opinion for PCT/US2004/001146 (WO 2004/064736)	
	AV	LOBL, 1979, "1-(2,4-Dicholorobenzyl)-1H-Indazole-3Carboxylic Acid (DICA), an Exfoliative Antispermatogenic Agent in the Rat" Arch Andrology 2:353-63.	
	AW	SHIDAIFAT et al, 1997, "Gossypol arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle" Anticancer Res. 17:1003-9.	
	AX	CHANG, 1997, "Gossypol induces spermidine/spermine N1-acetyltransferase in canine prostate epithelial cells" Biochem Biophys Res Commun. 231:383-8.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.